# PATENT COOPERATION TREATY

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From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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# PCT

## WRITTEN OPINION

(PCT Rule 66)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 21.06.2000 |
| Applicant's or agent's file reference: M0656/7046WO | **REPLY DUE** **within 3 month(s)** from the above date of mailing |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US99/19841 | 27/08/1999 | 27/08/1998 |

International Patent Classification (IPC) or both national classification and IPC
C12N15/60

Applicant
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.



2. This opinion contains indications relating to the following items:

| | | |
|---|---|---|
| I | ☒ | Basis of the opinion |
| II | ☒ | Priority |
| III | ☒ | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| IV | ☒ | Lack of unity of invention |
| V | ☒ | Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| VI | ☐ | Certain document cited |
| VII | ☐ | Certain defects in the international application |
| VIII | ☒ | Certain observations on the international application |



3. The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

**If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27/12/2000.

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Authorized officer / Examiner
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## I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-77 as originally filed

**Claims, No.:**

1-57 as originally filed

**Drawings, sheets:**

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has ~~been established as if no priority had been claimed~~ due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

## I. Basis

The documents mentioned in the present written opinion / International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

Sequence listing pages 1-8 are also included in the basis of the present assessment.

## II. Priority

The entire subject-matter of the present application appears to be entitled to priority from US application number 60/098153 (08.10.99). Hence, document D4 is not relevant prior art.

## III. No Opinion

No opinion can be given for those claims for which no International Search Report has been established (i.e. claims 22-29, 30(part), 32, (33-45)(part)).

## IV. Lack of Unity

The present application comprises 2 invention groups as set out in the International Search Report. Preliminary Examination can only be carried out on invention group I - modified heparinase II and matter relating thereto (claims 1-21, 30(part), 31, (33-45)(part), 46-57).

Invention group I is further considered intrinsically non-unitary. Mutants of the kind claimed by applicant are specified in the prior art. Hence, no common inventive concept would appear to link the claimed mutants. Applicant will have to eventually limit himself to a specific mutant. However, for practical reasons, this matter shall not be addressed in the International Phase.

## V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability

- **Novelty (Art.33(2) PCT)**

D2 is the closest prior art. D2 discloses various Heparinase II mutants in which cysteine residues have been modified. Modifications of individual histidine residues at one of positions 48, 238, , 249, 252, 347, 440, 473, 579, 682, to alanine were tested. Several mutants were void of enzymatic activity to either heparin or heparin sulphate (238, 406, 408, 451, 579). Mutants 252, 347 and 440, however, displayed differential activity towards heparin or heparin sulphate. The H347A mutant showed a marked decrease in activity (suggested to be due to proximity to cysteine 348). H440A has a reduced activity towards heparin. Precise quantitative data relating to the activity of the different mutants is not given. The document does not suggest medical applications yet suggests that mutants may be useful in developing heparinase II as a biological tool.

Until proven otherwise by the applicant, D2 is cited as novelty-destroying against the following claims (applicant is also referred to section on clarity): 1-5, 8-13, 16, 17, 20, 21, 30, 31, 46, 47, 52, 55-57. Indeed certain of these claims specifically refer to products already disclosed in D2 (claims 13, 16, 17, 31, 52).

D1 discloses the sequence of Heparinase II and recombinant expression thereof (example 7). No mutants with modified activities are disclosed. Hence, D1 does not anticipate any of the present claims.

- **Inventive Step (Art.33(3) PCT)**

With regard to uses of Heparinases (including potential medical uses), it is noted that given the knowledge of the possible role of hesparinases and their substrates in various disease states (see for example introduction of D1), and further in view of the fact that applicant has not been adding to the medical knowledge in the field, claims to medical uses of heparinase mutants could only be considered inventive where the mutants are inventive per se. The same applies to trivial matter such as pharmaceutical compositions or immobilized enzymes.

Claims 14, 15 and 49 relate specifically to C348 mutants. D2 already implicates this position as a potential active site residue (p.10166, col.2). Hence, mutants at

this position would be obvious to make for the purpose of testing whether the implication is correct.

Since no inventive mutants are identified, inventive step is not acknowledged for any of the claims.

- **Industrial Applicability (Art.33(4) PCT)**

For the assessment of the present claims 30-32, 35-44, 46, 47, 49 and 50 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 30-32, 35-44, 46, 47, 49 and 50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VIII. **Certain observations**

- **Clarity (Art.6 PCT)**

The term "product profile" is considered technically unclear.

The majority of the claims can be considered unclear since they relate to modified enzyme defined by the result to be achieved. Obtaining an enzyme with a somehow modified substrate specificity / reaction rate is the problem which applicant addresses with the claimed subject-matter. The claims need to specify the solution to the problem i.e. how the problem was overcome (in this case by introducing specific mutations). Further, claims need to clearly distinguish the claimed subject-matter from the prior art. In the present case, it is unclear which

of applicants mutations and which in the prior art (which overlaps substantially) can be considered to meet the specified "product profile" alterations. Novelty cannot be acknowledged for any of the claims where this is unclear. Indeed, given that applicants mutants were mainly known in the prior art and that it is to be assumed that the claims are drafted according to the types of effect achieved by these mutants, it would appear very likely that a substantial number of the claims are anticipated be the mutants already disclosed in D2..

3. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 22-29, 30(part), 32, (33-45)(part),

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 22-29, 30(part), 32, (33-45)(part).

**IV. Lack of unity of invention**

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

**see separate sheet**

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-21, 30(part), 31, (33-45)(part), 46-57 .

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims | 1-5, 8-13, 16, 17, 20, 21, 30, 31, 46, 47, 52, 55-57 |
| Inventive step (IS) | Claims | 1-21, 30, 31, 33-45, 46-57 |
| Industrial applicability (IA) | Claims | 30-32, 35-44, 46, 47, 49 and 50 |

2. Citations and explanations

   **see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

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# Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.